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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,321	KALLIES ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-34 and 37-47* is/are pending in the application.

4a) Of the above claim(s) *28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-27,30-34 and 37-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/29/2009 has been entered.

Claims 6, 7, 35 and 36 have been cancelled. Claims 28 and 29 have been withdrawn. Claims 20, 22 and 37 have been amended.

Claims 1-5, 8-27, 30-34 and 37-47 are under examination.

2. The objection to claim 37 for containing minor informalities is withdrawn in response to Applicant's amendment to the claim filed on 09/29/2009.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-5, 8-27, 30-34 and 37-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glimcher et al. (PGPUB 2002/0059652, of record), in view of each

Shaffer et al. (Immunity, 2002, 17: 51-62, of record), Pol et al. (Journal of Biomolecular Screening, 2002, 7: 325-332, of record), and Mountford et al. (Proc. Natl. Acad. Sci. USA, 1994, 91: 4303-4307, of record).

Glimcher et al. teach a method of *in vitro* or *in vivo* screening for agonists or antagonists of terminal differentiation of B- or T-cells, the method comprising contacting a test compound with B- or T-cells, wherein the B- or T-cells are ASC or $CD4^+$cells and could be of mouse origin, and wherein the test compound modulates the activity of XBP-1 transcription factor in the B- or T-cells (claims 1, 8-16, 30, 37, 38-43) (Abstract; p. 1, paragraphs 0004 and 0006; p. 2, paragraph 0008; p. 3, paragraphs 0019 and 0021; p. 4, paragraph 0031; p. 5, paragraphs 0042 and 0053; p. 11, paragraph 0097).

Glimcher et al. do not teach screening for compounds capable of modulating Blimp-1 activity (claims 1 and 30). However, they do teach that the XBP-1 transcription factor acts downstream of Blimp-1 (p. 24-25, paragraphs 0214 and 0215). Additionally, Shaffer et al. teach that Blimp-1 is the master regulator of plasma cells terminal differentiation, wherein Blimp acts by allowing the expression of specific transcription factors such as XBP-1 (Abstract, p. 56, Fig. 3, p. 59, Fig. 7, p. 60, column 1, last paragraph, column 2). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Glimcher et al. by substituting their XBP-1 with Blimp-1 to achieve the predictable result of screening for agonists or antagonists of terminal differentiation of B- or T-cells.

Glimcher et al. and Shaffer et al. do not teach inserting a nucleic acid encoding a reporter molecule into an intron of the *blimp* locus to obtain a modified *blimp* allele

comprising the Blimp coding sequences and the reporter under the control of the endogenous *blimp* regulatory elements (claims 1-3 and 30-32). However, doing such was suggested by the prior art. For example, Pol et al. teach that high-throughput screening methods require readouts other than determining the level or activity of the gene of interest. Pol et al. suggest using homologous recombination to place a reporter such as GFP under the control of the endogenous regulatory elements of the gene of interest, wherein the detection of the reporter indicates a cellular phenotype (claims 17 and 19) (Abstract; p. 325, column 1; p. 326, column 1; p. 327, column 2, third and fourth full paragraphs; p. 331, paragraph spanning columns 1 and 2). It is noted that, at the time the invention was made, homologous recombination to obtain cells comprising homozygous or heterozygous modifications was routine in the prior art. For example, Mountford et al. teach using homologous recombination in ES cells to place reporters under the control of regulatory sequences of endogenous genes of interest with or without modifying the endogenous gene, wherein insertion could be within an exon or within an intron (claims 3, 18, and 32) (Abstract, p. 4303, column 2 and Fig. 1). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Glimcher et al. and Shaffer et al. by using homologous recombination to place GFP into an intron of the *blimp* allele to achieve the predictable result of obtaining a genetically modified cell suitable for high-throughput screening of test agents capable of modulating Blimp-1 activity. It is noted that by going so, one of skill in the art would have used a targeting vector as recited in claims 44-47. Additionally, by practicing the screening method according to the combined teachings of

Glimcher et al., Shaffer et al., Pol et al., and Mountford et al., one of skill in the art would also have practiced a method of monitoring a B or T-cell, wherein detection of the reporter indicates the commitment of the B or T-cell to terminally differentiate (claims 20-27).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that, as supported by the § 1.132 Declaration of Dr. Nutt (attached), the Examiner's rationale underlying her conclusion that it would have been obvious to modify the cells and method of Glimcher by substituting XBP-1 with Blimp-1 is flawed. Further, the Examiner's combination of the references is improper. Moreover, even assuming that the teachings of the references were to be combined, the results achieved by the present invention were still unexpected to those skilled in the art.

Applicant argues that XBP-1 is not necessarily downstream of Blimp-1. The Examiner refers to [0214]-[0215] of Glimcher and to Shaffer in support of the notion that XBP-1 acts downstream of Blimp- 1. Applicant directs the Examiner's attention to the Declaration, paragraphs 4-5, where Dr. Nutt testified that based on a careful reading of Glimcher and Shaffer, and other references available at the relevant time, it was not possible for one skilled in the art to conclude that XBP-1 acts specifically downstream of Blimp-1. In fact, XBP-1 has been shown to be expressed both upstream and downstream of Blimp-1. In his 132 Declaration, Applicant submits that, based on a

careful reading of Glimcher and Shaffer and other references available at the relevant time, it was not possible for one skilled in the art to conclude that XBP-1 acts specifically downstream of Blimp-1. In support of the argument above, the 132 Declaration states that: **(a)** as opposed to Blimp-1, XBP-1 is ubiquitously expressed; **(b)** Shaffer states that the Blimp-1 gene alone is insufficient to achieve the high XBP-1 expression characteristic of plasma cells; this confirms that Blimp-2 is not equivalent to XBP-1 as a marker of B-cell terminal differentiation; **(c)** Shaffer uses transformed cell lines; **(d)** Reimold et al. (Exhibit 3) teach XBP-1 can be induced before the initiation of the terminal differentiation and that it can also function during terminal differentiation; in contrast, the instant invention teaches that Blimp-1 only functions downstream of the initiation of terminal differentiation (p. 66, line 29 through p. 67, line 4); **(e)** that Fig. 3 in Iwakoshi et al. (Exhibit 4) shows that XBP-1 was induced at time point 0, while Blimp-1 was not (i.e., XBP-1 was induced prior to Blimp-1); and **(f)** Shapiro-Shelef et al, (Exhibit 5) show that XBP-1 expression was reduced in Blimp-$1^{-/-}$ (also called Prdm$1^{-/-}$) B-cells, yet enforced expression of XBP- 1 did not compensate for the absence of Blimp-1; therefore XBP-1 is not likely to be in the same pathway as Blimp-1. Applicant's opinion is that the absence of high XBP-1 expression in the Blimp-$1^{-/-}$ B cells was due to the impaired formation of plasma cells without Blimp-1 and hence expression of XBP-1 and any other genes highly expressed in plasma cells was lost.

Applicant argues that the genetically modified cells disclosed by Glimcher include animals/cells which lack XBP-1 (abstract and paragraphs [0004], [0011], [0083], [0091], [0178] and [0214]), have over-expressed XBP-1 in conjunction with a reporter gene

responsive to the XBP-1 protein (paragraphs [0006] and [0214]), have over-expressed XBP-1 (paragraphs [0031], [0053], [0068] and [0073]), have an XBP-1 transgene driven by a liver-specific promoter (paragraph [0011]), or have an altered XBP-1 (paragraph [0082]). Applicant submits that modifying the cells and methods of Glimcher, as suggested by the Examiner, would result in the generation of a knockout Blimp mouse or cells lacking Blimp-1. See the abstract and paragraphs [0004], [0011], [0083], [0091], [0178] & [0214] of Glimcher). Alternatively, one would obtain (1) cells which over-express Blimp-1 in conjunction with a reporter gene responsive to the Blimp-1 protein (paragraphs [0006] and [0214]); (2) cells which over-express Blimp-i (paragraphs [0031], [0053], [0068] and [0073]); (3) cells which have a Blimp-1 transgene driven by a liver-specific promoter (paragraph [0011]), or (4) cells which have an altered Blimp-1 (paragraph [0082]) in contrast to wild type Blimp-1. However, none of these alternatives would provide a cell or non-human organism comprising such a cell containing a genetic modification characterized by the insertion of a reported gene in an endogenous Blimp-1 allele, as presently claimed. Importantly, there is no disclosure or suggestion in Glimcher of a modified Blimp gene being endogenous Blimp inserted with a reporter driven by endogenous Blimp regulatory elements, as presently claimed. The Examiner has attempted to rely on Pol and Mountford to cure this fundamental deficiency of Glimcher, because Pol allegedly teaches placing a reporter under control of the endogenous regulatory elements of a gene of interest wherein the detection of the reporter indicates a cellular phenotype, and Mountford allegedly teaches the relevant methodology to do so. However, Applicant submits that the premise for Pol's placement

of a reporter under control of the endogenous regulatory elements of a gene of interest was that the genes of interest had already been identified to be specifically expressed in lesional psoriatic skin, but not in normal skin; i.e., expression of these genes was a surrogate marker for psoriasis. In the present case, absent the recognition that terminal differentiation of cells is linked to expression of Blimp-1, which is provided uniquely by the present invention, those skilled in the art would not have been motivated to rely on Pol and place a reporter gene under control of endogenous Blimp regulatory elements. Applicant submits that the Examiner has engaged in impermissible hindsight construction by combining the teachings of Glimcher with Pol and Mountford.

Applicant argues that the results achieved by the instant invention are unexpected. As Dr. Nutt testified (paragraph 6), prior to the present invention, there were no good markers in the art for fully differentiated antibody secreting cells ("ASCs" or plasma cells). It has been a unique recognition provided by the present invention that not only substantially all ASCs express Blimp-1 in a cell population, but also no pre-plasma/ASC cells express Blimp-1. See pages 65-67 (Examples 3-4) of the specification. Similar expression profiles were also observed with terminally differentiated T cells although expression of Blimp-1 was at a lower level. As Dr. Nutt further explained (paragraph 7), the specific association of the expression of Blimp in plasma cells - i.e., expression in all plasma cells and lack of expression in earlier stages of B and T-cell differentiation, makes Blimp an especially useful marker for identifying modulators of terminal differentiation. In contrast, XBP-1 is expressed upstream and downstream of signals that drive plasma cell differentiation (see the Nutt Declaration).

Therefore, identifying modulators of endogenous XBP-1 expression would not appear to provide a selective method for screening for modulators of terminal differentiation. Furthermore, if only a proportion of cells endogenously express XBP-1 and only for some time, it would be more difficult to identify modulators of endogenous expression. In paragraph 8, Dr. Nutt testified that prior to the present invention, targeting of Blimp was considered to potentially suffer from the same problems. It was not known and could not have been predicted that all fully differentiated antibody secreting cells (ASCs or plasma cells) express Blimp-1. It is evident that endogenous Blimp expression consistently and only in terminal differentiated haematopoietic cells makes the claimed assays, and the related cells and vectors, much more improved over the XBP-1 based methodology disclosed by Glimcher. The results achieved by the present invention are not only superior but also unexpected to those skilled in the art.

Therefore, applicant requests the withdrawal of the rejection.

Applicant's arguments and Declaration are acknowledged; however, they are not found persuasive for the following reasons:

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant's arguments and 132 Declaration stating that XBP-1 is not necessarily downstream of Blimp-1 are not found persuasive. The art as a whole (including the references submitted by Applicant with his 132 Declaration) teaches that XBP-1 expression is repressed by Pax-5 and that B-cell differentiation is initiated only when Blimp-1 induces XBP-1 expression by repressing Pax-5; the prior art teaches that XBP-1 is not induced in the absence of Blimp-1 in B-cells, (see Shaffer et al., p. 51, column 2, p. 60, column 1, second full paragraph; Shapiro-Shelef, Exhibit 5 in Applicant's 132 Declaration, p. 611, column 2, p. 616, paragraph bridging columns 1 and 2). Therefore, XBP-1 necessarily acts downstream of Blimp-1 in the context of B-cell.

The statements in the 132 Declaration are not found persuasive for the following reasons: **(a)** just because, as opposed to Blimp-1, XBP-1 is ubiquitously expressed does not mean that XBP-1 does not act downstream of Blimp-1 in the context of B-cells. The prior art clearly teaches that XBP-1 is not induced in the absence of Blimp-1 in B-cells (see above); **(b)** just because Shafer states that Blimp-1 is not sufficient to induce the elevated XBP-1 levels characteristic of plasma cells does not mean that XBP-1 is not downstream of Blimp-1. The art as a whole teaches that the initial trigger of XBP-1 expression in B-cells is Blimp-1, as XBP-1 expression in B-cells is not induced in the absence of Blimp-1. With respect to the elevated XBP-1 levels characteristic of plasma cells, these are achieved after gene induction by Blimp-1 via post-transcriptional regulation, wherein the post-transcriptional regulation results in a spliced variant which

is more active and more stable (hence higher levels) than the unspliced XBP-1 which is initially induced by Blimp-1 (see *Shaffer*, p. 60, column 1, last paragraph; *Shapiro-Shelef*, p. 616, column 1, last paragraph; *Gass et al.*, J. Biol. Chem., 2002, 277, 50: 49047-49054, Abstract, p. 49047, column 2, second full paragraph, p. 49048, column 2, last paragraph, p. 49049, column 1, p. 49053, column 1, second full paragraph); **(c)** Applicant argues that Shaffer uses transformed B-cells and does not address whether Blimp-1 is upstream of XBP-1 in the context of B-cells. Applicant states that, in his opinion, one of skill in the art would not have drawn conclusions that XBP-1 acts downstream of Blimp-1 based on results using transformed B-cells alone. Applicant's opinion is acknowledged; however, Applicant's opinion does not replace evidence when evidence is necessary (it is interesting to note that, in traversing the instant rejection, Applicant relies on results obtained from experiments with transformed B-cells alone); **(d)** Applicant argues that, in contrast to the instant specification which teaches that Blimp-1 only functions downstream of the initiation of terminal differentiation, Fig. 2 in Reimold (Exhibit 3) shows that XBP-1 can be induced before the initiation or during terminal differentiation. This is incorrect. Reimold does not teach that XBP-1 can be induced before the initiation of terminal differentiation. Reimold only teaches that XBP-1 acts upstream or downstream of signals that drive plasma cells differentiation, which are not the same with initiation of terminal differentiation. This is supported by Fig. 2A in Reimold, which shows that, in normal B-lymphocytes, XBP-1 is induced after the initiation of terminal differentiation (i.e., like Blimp-1, XBP-1 functions downstream of the initiation of terminal differentiation). Clearly, Reimold's teachings refer to differentiation

signals which occur after the initiation of terminal differentiation; **(e)** Fig. 3 in Iwakoshi (Exhibit 4) shows the results with the neoplastic B-cell line BCL1 which, as opposed to normal B-cell or the other B-cell lines, express basal levels of XBP-1 which do not change upon stimulation (see p. 323, column 2, second full paragraph). In fact, Figs. 1A and B in Iwakoshi show that XBP-1 is expressed in B-cells only after the initiation of terminal differentiation; this is consistent with the results presented in Reimold's Fig. 2A; **(f)** according to Applicant, since Shapiro-Shelef (Exhibit 5) shows that XBP-1 expression was reduced in Blimp-$1^{-/-}$ B-cells, yet enforced expression of XBP- 1 did not compensate for the absence of Blimp-1, XBP-1 is not likely to be in the same pathway as Blimp-1. Again this is just an opinion not supported by any evidence. Shapiro-Shelef does teach that Blimp-1 induces XBP-1 (p. 611, column 2, p. 616, column 1, last paragraph). Shapiro-Shelef's teaching that XBP- 1 did not compensate for the absence of Blimp-1 does not mean that XBP-1 is not induced by Blimp-1 (i.e., downstream of Blimp-1) but rather that, beside XBP-1, Blimp-1 activates other genes necessary for terminal differentiation (see p. 616, column 2, first full paragraph).

Based on the teachings in the art as a whole, one of skill in the art would have known that XBP-1 acts downstream of Blimp-1 and that, similar to XBP-1, Blimp-1 is a marker of B-cell terminal differentiation.

It is noted that Applicant individually argues. In response to Applicant's arguments against Glimacher individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck &*

Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Glimacher does not have to teach each and every claim limitation. If he did, this would have been anticipation and not an obviousness-type rejection.

Applicant argues that, absent the recognition that terminal differentiation is linked to Blimp-1 expression, which is provided only by the instant invention, one of skill in the art would not have been motivated to rely on Pool and place the reporter gene under the control of the endogenous Blimp-1 promoter. This argument is not found persuasive because, as demonstrated above, Applicant was not the first to recognize that terminal differentiation of B-cells depends on Blimp-1. Such is taught by the prior art.

Applicant's argument of unexpected results is not found persuasive. Applicant only described an inherent property of B-cells at different stages of differentiation. That all plasma cells, but not pre-plasma cells, express Blimp-1 is not unexpected; the prior art teaches such (see *Shaffer*, p. 51, paragraph bridging columns 1 and 2; *Turner et al.*, Cell, 1994, 77: 297-308, p. 297, column 2, second full paragraph; *Angelin-Duclos et al.*, J. Immunol., 2000, 165: 5462-5471, p. 55463, column 1, first paragraph).

Applicant argues that, since XBP-1 is not necessarily downstream of Blimp-1, the claimed assay based on Blimp-1 is superior over the assay based on XBP-1. This argument is not found persuasive because, as noted above, XBP-1 is only induced by Blimp-1 in B-cells, i.e., XBP-1 is downstream of Blimp-1; therefore, XBP-1 and Blimp-1 are equivalent as markers for B-cell differentiation.

Conclusion

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Gass et al. (J. Biol. Chem., 2002, 277, 50: 49047-49054) was cited in response to Applicant's argument that XBP-1 is not necessarily downstream of Blimp-1. The reference provides evidence that XBP-1 is downstream of Blimp-1. Turner et al. (Cell, 1994, 77: 297-308) and Angelin-Duclos et al. (J. Immunol., 2000, 165: 5462-5471) were cited in response to Applicant's argument of unexpected results. The references demonstrate that Applicant's observation that all plasma cells (but not pre-plasma cells) express Blimp-1 was not unexpected since such was already known in the prior art.

6. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633